

7163 10 JUL 20 1990

April 26, 2000

Dockets Management Branch (HFA-305)
Food and Drug Administration
5600 Fishers Lane
Room 4-62
Rockville, MD 20857

CITIZEN PETITION

The undersigned submits this Petition, pursuant to Section 505(j)(2)(c) of the Federal Food, Drug, and Cosmetic Act (the Act) and 21 C.F.R. Sections 314.93(b) and 10.30 of the Food and Drug Administration's regulations, to request the Commissioner of Food and Drugs to make a determination that a certain opioid analgesic elixir drug product is suitable for filing under an abbreviated new drug application (ANDA).

A. Action Requested

Petitioner requests that the Commissioner of Food and Drugs make a determination that an abbreviated new drug application (ANDA) is suitable for elixir containing 10 mg hydrocodone bitartrate/650 mg acetaminophen per 30 mL.

B. Statement of Grounds

The Drug Price Competition and Patent Term Restoration Act of 1984 ("the Waxman-Hatch Act") extends eligibility for the submission of ANDA's to certain drug products identical to those approved via new drug applications, as identified in the *List of Approved Drug Products with Therapeutic Equivalence Evaluations* ("the Orange Book") published by the Food and Drug Administration. Where the proposed drug product differs from the "listed drug" in one or more respects, a person may petition the Agency, under section 505(j)(2)(c) of the Act, for a determination that the proposed drug is suitable to be submitted as an ANDA.

The listed drug product that forms the basis for this petition Watson, 10 mg/650 mg (ANDA 40-094). See Orange Book, page 3-5, at Exhibit A. To the best of petitioner's knowledge, applicable U.S. patents with respect to the drug substances, hydrocodone bitartrate and acetaminophen, have expired.

00P-1243

CP2

The proposed drug product differs from the listed drug products only in regard to dosage form (elixir instead of tablet). Otherwise, the proposed drug product is identical with respect to active ingredients, strength, route of administration, and conditions of use.

The availability of an elixir dosage form of hydrocodone bitartrate and acetaminophen would provide a valuable dosage alternative, particularly for those patients who have trouble swallowing tablets, the geriatric population and other situations where a liquid dosage would be preferred.

The proposed product's dosage form is the same as several other types of approved opioid analgesic drugs which are available in liquid form. For instance, Dilaudid (hydromorphone hydrochloride), NDA 19891 (*Orange Book* at 3-182); and Lortab Elixir (Hydrocodone Bitartrate and Acetaminophen Elixir), ANDA 81051 (*Orange Book* at 3-4) attached as Exhibit B.

In view of the availability of other approved opioid analgesics as elixirs and an appropriate patient base for such a form (e.g., geriatric patients), the healthcare community would benefit from the availability of an elixir dosage form of hydrocodone bitartrate and acetaminophen 10 mg/650 mg per 30 mL. The proposed product contains the same active ingredients, at the same strength and route of administration, and would be labeled with the same conditions of use as the listed 10mg/650 mg tablets [See Exhibits C (Side-By-Side comparison of Watson insert and proposed insert) and D (Side-By-Side comparison of Watson labeling and proposed labeling)] and packaged in an appropriate container-closure system (See Exhibit E).

Based on the foregoing, Petitioner believes that an elixir dosage form of hydrocodone bitartrate and acetaminophen 10 mg/650 mg per 30 mL warrants a finding of ANDA suitability and that the commissioner should grant permission for the filing of an ANDA for a hydrocodone bitartrate and acetaminophen elixir in the strength of 10mg/650 mg per 30 mL.

C. Environmental Impact

A categorical exclusion is claimed as the granting of this Petition will result in an ANDA for a drug product that is consistent with the parameters for exclusion established in 21 C.F.R. 25.24(c)(1).

D. Economic Impact

Information under this section will be submitted if requested by the Commissioner following review of this Petition.

E. Certification

The undersigned certifies that, to the best knowledge and belief of the undersigned, this Petition includes all information and views upon which the Petition relies, and that it includes representative data and information known to the Petitioner which are unfavorable to the Petition.

PHARMACEUTICAL ASSOCIATES, INC.

By: Kaye B. McDonald
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Greenville, SC 29605
(864) 277-7282 Ext. 230

Enclosures:

- A. *Orange Book*, page 3-5.
- B. *Orange Book*, pages 3-4 and 3-182.
- C. Side-By-Side comparison of Watson package insert (December 1997) and proposed insert.
- D. Side-By-Side comparison of Watson and labeling and proposed labeling for hydrocodone bitartrate and acetaminophen 10 mg/650 mg per 30 mL elixir.
- E. Description of container and closure system for hydrocodone bitartrate and acetaminophen 10 mg/650 mg per 30 mL elixir.

Exhibit A

PRESCRIPTION DRUG PRODUCT LIST

3-5

ACETAMINOPHEN; HYDROCODONE BITARTRATE

TABLET; ORAL	
HYDROCODONE BITARTRATE AND ACETAMINOPHEN	
AA VINTAGE PHARMS	650MG; 10MG
AA	750MG; 7.5MG
AA WATSON LABS	500MG; 2.5MG
AA	500MG; 2.5MG
AA	500MG; 5MG
AA	500MG; 5MG
AA	500MG; 7.5MG
AA	500MG; 7.5MG
AA	500MG; 10MG ✓
AA	650MG; 7.5MG
AA	650MG; 7.5MG
AA	650MG; 10MG ✓
AA	650MG; 10MG
AA	750MG; 7.5MG
AA	750MG; 7.5MG
AA ZENITH GOLDLINE	500MG; 5MG
AA LORTAB	500MG; 5MG
AA MALLINCKRODT	500MG; 10MG
AA + UCB	325MG; 5MG
AA NORCO	325MG; 10MG ✓
AA + WATSON LABS	
AA VICODIN	500MG; 5MG
AA + KNOLL PHARM	

N40143 001
FEB 22, 1996
N40157 001
APR 12, 1996
N40123 003
MAR 04, 1996
N81079 001
AUG 30, 1991
N40122 001
MAR 04, 1996
N89883 001
DEC 01, 1988
N40123 004
MAR 04, 1996
N81080 001
AUG 30, 1991
N40148 002
FEB 14, 1997
N40094 001
SEP 29, 1995
N40123 001
MAR 04, 1996
N40094 002
SEP 29, 1995
N40123 002
MAR 04, 1996
N40122 002
MAR 04, 1996
N81083 001
AUG 30, 1991
N89696 001
APR 21, 1988
N87722 001
JUL 09, 1982
N40100 001
JAN 26, 1996
N40099 001
JUN 25, 1997
N40148 001
FEB 14, 1997
N88058 001
JAN 07, 1983

ACETAMINOPHEN; HYDROCODONE BITARTRATE

TABLET; ORAL	
VICODIN ES	
AA + KNOLL PHARM	750MG; 7.5MG
VICODIN HP	
AA KNOLL PHARM	660MG; 10MG

N89736 001
DEC 09, 1988

N40117 001
SEP 23, 1996

ACETAMINOPHEN; OXYCODONE

CAPSULE; ORAL	
OXYCODONE AND ACETAMINOPHEN	
AA HALSEY	500MG; 5MG

N40219 001
JAN 22, 1998

ACETAMINOPHEN; OXYCODONE HYDROCHLORIDE

CAPSULE; ORAL	
OXYCODONE AND ACETAMINOPHEN	
AA AMIDE PHARM	500MG; 5MG
AA MALLINCKRODT	500MG; 5MG
AA VINTAGE PHARMS	500MG; 5MG
AA WATSON LABS	500MG; 5MG
AA ROXILOX	500MG; 5MG
AA ROXANE	500MG; 5MG
AA TYLOX	500MG; 5MG
AA + JOHNSON RW	500MG; 5MG

N40199 001
DEC 30, 1998
N40257 001
AUG 04, 1998
N40106 001
JUL 30, 1996
N40234 001
OCT 30, 1997

N40061 001
JUL 03, 1995

N88790 001
DEC 12, 1984

SOLUTION; ORAL	
ROXICET	
ROXANE	325MG/5ML; 5MG/5ML

N89351 001
DEC 03, 1986

TABLET; ORAL	
OXYCET	
AA MALLINCKRODT	325MG; 5MG

N87463 001
DEC 07, 1983

OXYCODONE AND ACETAMINOPHEN	
AA DURAMED	325MG; 5MG

N40272 001
JUN 30, 1998

Exhibit B

PRESCRIPTION DRUG PRODUCT LIST

3-4

ACETAMINOPHEN; HYDROCODONE BITARTRATE

ELIXIR; ORAL		HYDROCODONE BITARTRATE AND ACETAMINOPHEN
AA	+	MIKART
		500MG/15ML; 7.5MG/15ML
		500MG/15ML; 5MG/15ML
	+	500MG/15ML; 5MG/15ML
AA		PHARM ASSOC
		500MG/15ML; 7.5MG/15ML
TABLET; ORAL		
AA		ANEXSIA
		MALLINCKRODT
		500MG; 5MG
AA	+	ANEXSIA 10/660
		MALLINCKRODT
		660MG; 10MG
AA		ANEXSIA 7.5/650
		MALLINCKRODT
		650MG; 7.5MG
AA		CO-GESIC
		SCHWARZ PHARMA
		500MG; 5MG
AA		HY-PHEN
		ASCHER
		500MG; 5MG
AA		HYDROCODONE BITARTRATE AND ACETAMINOPHEN
		ENDO PHARMS
		500MG; 5MG
		500MG; 7.5MG
		650MG; 7.5MG
		650MG; 10MG
		750MG; 7.5MG
		400MG; 5MG
		400MG; 7.5MG
		400MG; 10MG
AA		EON
		500MG; 5MG

✓ N81051 001
AUG 28, 1992
N81226 001
OCT 27, 1992
N89557 001
APR 29, 1992
N40182 001
MAR 13, 1998

N89160 001
APR 23, 1987

N40084 003
JUL 29, 1996

N89725 001
SEP 30, 1987

N87757 001
MAY 03, 1982

N87677 001
MAY 03, 1982

N40281 001
SEP 30, 1998

N40280 001
SEP 30, 1998

N40280 002
SEP 30, 1998

N40280 003
SEP 30, 1998

N40281 002
SEP 30, 1998

N40288 001
NOV 27, 1998

N40288 002
NOV 27, 1998

N40288 003
NOV 27, 1998

N40149 001
JAN 27, 1997

ACETAMINOPHEN; HYDROCODONE BITARTRATE

TABLET; ORAL

HYDROCODONE BITARTRATE AND ACETAMINOPHEN		
EON		750MG; 7.5MG
		500MG; 5MG
		650MG; 7.5MG
		650MG; 10MG
		750MG; 7.5MG
		500MG; 5MG
		500MG; 7.5MG
		500MG; 10MG
		750MG; 7.5MG
		500MG; 2.5MG
		500MG; 5MG
		500MG; 5MG
		500MG; 7.5MG
		650MG; 7.5MG
		650MG; 10MG
		500MG; 10MG
		650MG; 7.5MG
		500MG; 2.5MG
		500MG; 5MG
		500MG; 5MG
		500MG; 7.5MG
		650MG; 7.5MG

HALSEY

MALLINCKRODT

+ MIKART

PEACHTREE

UCB

VINTAGE PHARMS

N40149 002
JAN 27, 1997
N40236 001
SEP 25, 1997
N40240 002
NOV 26, 1997
N40240 001
NOV 26, 1997
N40236 002
SEP 25, 1997
N40084 002
JUN 01, 1995
N40201 001
FEB 27, 1998
N40201 002
FEB 27, 1998
N40084 001
JUN 01, 1995
N89698 001
AUG 25, 1989
N89271 001
JUL 16, 1986
N89697 001
JAN 28, 1992
N89699 001
AUG 25, 1989
N89689 001
JUN 29, 1988
N81223 001
MAY 29, 1992
N40210 001
AUG 13, 1997
N40134 001
NOV 21, 1996
N40144 002
APR 25, 1997
N89831 001
SEP 07, 1988
N89971 001
DEC 02, 1988
N40144 001
FEB 22, 1996
N40155 001
APR 14, 1997

PRESCRIPTION DRUG PRODUCT LIST

3-182

HYDROCORTISONE SODIUM SUCCINATE

INJECTABLE; INJECTION
SOLD-CORTEF

AP + PHARMACIA AND UPJOHN EQ 500MG BASE/VIAL
AP + EQ 1GM BASE/VIAL

N09866 003
N09866 004

HYDROCORTISONE VALERATE

CREAM; TOPICAL

HYDROCORTISONE VALERATE

AB COPLEY PHARM 0.2%

AB TARO 0.2%

WESTCORT

AB + WESTWOOD SQUIBB 0.2%

OINTMENT; TOPICAL

HYDROCORTISONE VALERATE

AB TARO 0.2%

WESTCORT

AB + WESTWOOD SQUIBB 0.2%

N74489 001
AUG 12, 1998
N75042 001
AUG 25, 1998

N17950 001

N75043 001
AUG 25, 1998

N18726 001
AUG 08, 1983

HYDROFLUMETHIAZIDE

TABLET; ORAL

DIUCARDIN

AB WYETH AYERST 50MG

AB HYDROFLUMETHIAZIDE
PAR PHARM 50MG

SALURON

AB + ROBERTS LABS 50MG

N83383 001

N88850 001
MAY 31, 1985

N11949 001

HYDROFLUMETHIAZIDE; RESERPINE

TABLET; ORAL

RESERPINE AND HYDROFLUMETHIAZIDE

BP PAR PHARM 50MG;0.125MG

SALUTENSIN

BP + ROBERTS LABS 50MG;0.125MG

SALUTENSIN-DEMI

ROBERTS LABS 25MG;0.125MG

N88907 001
SEP 20, 1985

N12359 003

N12359 004

HYDROMORPHONE HYDROCHLORIDE

INJECTABLE; INJECTION

DILAUDID-HP

AP + KNOLL PHARM 10MG/ML

+ 250MG/VIAL

HYDROMORPHONE HCL

AP ABBOTT 10MG/ML

AP STERIS 10MG/ML

SOLUTION; ORAL

DILAUDID

AA + KNOLL PHARM 5MG/5ML

HYDROMORPHONE HCL

AA ROXANE 5MG/5ML

TABLET; ORAL

DILAUDID

AB + KNOLL PHARM 8MG

HYDROMORPHONE HCL

AB ROXANE 8MG

N19034 001
JAN 11, 1984
N19034 002
AUG 04, 1994

N74598 001
JUN 19, 1997
N74317 001
AUG 23, 1995

N19891 001
DEC 07, 1992

N74653 001
JUL 29, 1998

N19892 001
DEC 07, 1992

N74597 001
JUL 29, 1998

HYDROXOCOBALAMIN

INJECTABLE; INJECTION

HYDROXOCOBALAMIN

+ STERIS 1MG/ML

N85998 001

HYDROXYAMPHETAMINE HYDROBROMIDE

SOLUTION/DROPS; OPHTHALMIC

PAREDRIE

+ PHARMICS 1%

N00004 004

Exhibit C

= Change due to dosage form

ANDA Product

Hydrocodone: Following a 10 mg oral dose of hydrocodone administered to five adult male subjects, the mean peak concentration was 23.6 ± 5.2 ng/mL. Maximum serum levels were achieved at 1.3 ± 0.3 hours and the half-life was determined to be 3.8 ± 0.3 hours. Hydrocodone exhibits a complex pattern of metabolism including O-demethylation, N-demethylation and 6-keto reduction to the corresponding 6- α - and 6- β -hydroxymetabolites.

See OVERDOSAGE for toxicity information.

Acetaminophen: Acetaminophen is rapidly absorbed from the gastrointestinal tract and is distributed throughout most body tissues. The plasma half-life is 1.25 to 3 hours, but may be increased by liver damage and following overdosage. Elimination of acetaminophen is principally by liver metabolism (conjugation) and subsequent renal excretion of metabolites. Approximately 85% of an oral dose appears in the urine within 24 hours of administration, most as the glucuronide conjugate, with small amounts of other conjugates and unchanged drug.

See overdosage for toxicity information.

INDICATIONS AND USAGE

Hydrocodone and acetaminophen elixir is indicated for the relief of moderate to moderately severe pain.

CONTRAINDICATIONS

This product should not be administered to patients who have previously exhibited hypersensitivity to hydrocodone, acetaminophen, or any other component of this product.

WARNINGS

Respiratory Depression: At high doses or in sensitive patients, hydrocodone may produce dose-related respiratory depression by acting directly on the brain stem respiratory center. Hydrocodone also affects the center that controls respiratory rhythm, and may produce irregular and periodic breathing.

Head Injury and Increased Intracranial Pressure: The respiratory depressant effects of opioids and their capacity to elevate cerebrospinal fluid pressure may be markedly exaggerated in the presence of head injury, other intracranial lesions, or a pre-existing increase in intracranial pressure. Furthermore, opioids produce adverse reactions which may obscure the clinical course of patients with head injuries.

Acute abdominal Conditions: The administration of opioids may obscure the diagnosis or clinical course of patients with acute abdominal conditions.

Listed Drug

Hydrocodone: Following a 10 mg oral dose of hydrocodone administered to five adult male subjects, the mean peak concentration was 23.6 ± 5.2 ng/mL. Maximum serum levels were achieved at 1.3 ± 0.3 hours and the half-life was determined to be 3.8 ± 0.3 hours. Hydrocodone exhibits a complex pattern of metabolism including O-demethylation, N-demethylation and 6-keto reduction to the corresponding 6- α - and 6- β -hydroxymetabolites.

See OVERDOSAGE for toxicity information.

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See OVERDOSAGE for toxicity information.

INDICATIONS AND USAGE

Hydrocodone and acetaminophen tablets are indicated for the relief of moderate to moderate severe pain.

CONTRAINDICATIONS

This product should not be administered to patients who have previously exhibited hypersensitivity to hydrocodone or acetaminophen.

WARNINGS

Respiratory Depression: At high doses or in sensitive patients, hydrocodone may produce dose-related respiratory depression by acting directly on the brain stem respiratory center. Hydrocodone also affects the center that controls respiratory rhythm, and may produce irregular and periodic breathing.

Head Injury and Increased Intracranial Pressure: The respiratory depressant effects of narcotics and their capacity to elevate cerebrospinal fluid pressure may be markedly exaggerated in the presence of head injury, other intracranial lesions or a pre-existing increase in intracranial pressure. Furthermore, narcotics produce adverse reactions which may obscure the clinical course of patients with head injuries.

Acute Abdominal Conditions: The administration of narcotics may obscure the diagnosis or clinical course of patients with acute abdominal conditions.

= Brand Name |
Generic Name

ANDA Product

Listed Drug

PRECAUTIONS

General: Special Risk Patients: As with any opioid analgesic agent, **Hydrocodone Bitartrate and Acetaminophen Elixir** should be used with caution in elderly or debilitated patients, and those with severe impairment of hepatic or renal function, hypothyroidism, Addison's disease, prostatic hypertrophy, or urethral stricture. The usual precautions should be observed and the possibility of respiratory depression should be kept in mind.

Cough Reflex: Hydrocodone suppresses the cough reflex; as with all opioids, caution should be exercised when Hydrocodone Bitartrate and Acetaminophen Elixir is used postoperatively and in patients with pulmonary disease.

Information for Patients: Hydrocodone, like all opioids, may impair mental and/or physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery; patients should be cautioned accordingly.

Alcohol and other CNS depressants may produce an additive CNS depression, when taken with this combination product, and should be avoided.

Hydrocodone may be habit-forming. Patients should take the drug only for as long as it is prescribed, in the amounts prescribed, and no more frequently than prescribed.

Laboratory Tests: In patients with severe hepatic or renal disease, effects of therapy should be monitored with serial liver and/or renal function tests.

Drug Interactions: Patients receiving opioids, antihistamines, antipsychotics, antianxiety agents, or other CNS depressants (including alcohol) concomitantly with Hydrocodone Bitartrate and Acetaminophen Elixir may exhibit an additive CNS depression. When combined therapy is contemplated, the dose of one or both agents should be reduced.

The use of MAO inhibitors or tricyclic antidepressants with hydrocodone preparations may increase the effect of either the antidepressant or hydrocodone.

Drug/Laboratory Test Interactions: Acetaminophen may produce false-positive test results for urinary 5-hydroxyindoleacetic acid.

Carcinogenesis, Mutagenesis, Impairment of Fertility: No adequate studies have been conducted in animals to determine whether hydrocodone or acetaminophen have a potential for carcinogenesis, mutagenesis, or impairment of fertility.

PRECAUTIONS

General: Special Risk Patients: As with any opioid analgesic agent, hydrocodone bitartrate and acetaminophen tablets should be used with caution in elderly or debilitated patients, and those with severe impairment of hepatic or renal function, hypothyroidism, Addison's disease, prostatic hypertrophy, or urethral stricture. The usual precautions should be observed and the possibility of respiratory depression should be kept in mind.

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Hydrocodone may be habit-forming. Patients should take the drug only for as long as it is prescribed, in the amounts prescribed, and no more frequently than prescribed.

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= Brand Name /
Generic Name

ANDA Product

Listed Drug

Pregnancy:

Teratogenic Effects: Pregnancy category C: There are no adequate and well-controlled studies in pregnant women. Hydrocodone Bitartrate and Acetaminophen Elixir should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nonteratogenic Effects: Babies born to mothers who have been taking opioids regularly prior to delivery will be physically dependent. The withdrawal signs include irritability and excessive crying, tremors, hyperactive reflexes, increased respiratory rate, increased stools, sneezing, yawning, vomiting, and fever. The intensity of the syndrome does not always correlate with the duration of maternal opioid use or dose. There is no consensus on the best method of managing withdrawal.

Labor and Delivery: As with all opioids, administration of this product to the mother shortly before delivery may result in some degree of respiratory depression in the newborn, especially if higher doses are used.

Nursing Mothers: Acetaminophen is excreted in breast milk in small amounts, but the significance of its effects on nursing infants is not known. It is not known whether hydrocodone is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from hydrocodone and acetaminophen, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use: Safety and effectiveness in pediatric patients have not been established.

ADVERSE REACTIONS

The most frequently reported adverse reactions are lightheadedness, dizziness, sedation, nausea, and vomiting. These effects seem to be more prominent in ambulatory than in nonambulatory patients, and some of these adverse reactions may be alleviated if the patient lies down.

Other adverse reactions include:

Central Nervous System: Drowsiness, mental clouding, lethargy, impairment of mental and physical performance, anxiety, fear, dysphoria, psychic dependence, mood changes.

Gastrointestinal System: Prolonged administration of hydrocodone bitartrate and acetaminophen elixir may produce constipation.

Pregnancy:

Teratogenic Effects: Pregnancy Category C: There are no adequate and well-controlled studies in pregnant women. Hydrocodone Bitartrate and Acetaminophen Tablets should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nonteratogenic Effects: Babies born to mothers who have been taking opioids regularly prior to delivery will be physically dependent. The withdrawal signs include irritability and excessive crying, tremors, hyperactive reflexes, increased respiratory rate, increased stools, sneezing, yawning, vomiting, and fever. The intensity of the syndrome does not always correlate with the duration of maternal opioid use or dose. There is no consensus on the best method of managing withdrawal.

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ADVERSE REACTIONS

The most frequently reported adverse reactions are lightheadedness, dizziness, sedation, nausea, and vomiting. These effects seem to be more prominent in ambulatory than in nonambulatory patients, and some of these adverse reactions may be alleviated if the patient lies down.

Other adverse reactions include:

Central Nervous System: Drowsiness, mental clouding, lethargy, impairment of mental and physical performance, anxiety, fear, dysphoria, psychic dependence, mood changes.

Gastrointestinal System: Prolonged administration of hydrocodone bitartrate and acetaminophen tablets may produce constipation.

= Brand Name /
Generic Name

ANDA Product

Listed Drug

Genitourinary System: Ureteral spasm, spasm of vesical sphincters and urinary retention have been reported with opiates.

Respiratory Depression: Hydrocodone bitartrate may produce dose-related respiratory depression by acting directly on brain stem respiratory centers (see OVERDOSAGE).

Dermatological: Skin rash, pruritus.

The following adverse drug events may be borne in mind as potential effects of acetaminophen: allergic reactions, rash, thrombocytopenia, agranulocytosis.

Potential effects of high dosage are listed in the OVERDOSAGE section.

DRUG ABUSE AND DEPENDENCE

Controlled Substance: Hydrocodone Bitartrate and Acetaminophen Elixir is classified as a Schedule III controlled substance.

Abuse and Dependence: Psychic dependence, physical dependence, and tolerance may develop upon repeated administration of opioids; therefore, this product should be prescribed and administered with caution. However, psychic dependence is unlikely to develop when hydrocodone bitartrate and acetaminophen elixir is used for a short time for treatment of pain.

Physical dependence, the condition in which continued administration of the drug is required to prevent the appearance of a withdrawal syndrome, assumes clinically significant proportions only after several weeks of continued opioid use, although some mild degrees of physical dependence may develop after a few days of opioid therapy. Tolerance, in which increasingly large doses are required in order to produce the same degree of analgesia, is manifested initially by shortened duration of analgesic effect, and subsequently by decreases in the intensity of the analgesia. The rate of development of tolerance varies among patients.

OVERDOSAGE

Following an acute overdosage, toxicity may result from hydrocodone or acetaminophen.

Signs and Symptoms:

Hydrocodone: Serious overdose with hydrocodone is characterized by respiratory depression (a decrease in respiratory rate and/or tidal volume, Cheyne-Stokes respiration, cyanosis), extreme somnolence progressing to

Genitourinary System: Ureteral spasm, spasm of vesical sphincters and urinary retention have been reported with opiates.

Respiratory Depression: Hydrocodone bitartrate may produce dose-related respiratory depression by acting directly on brain stem respiratory centers (see OVERDOSAGE).

Dermatological: Skin rash, pruritus.

The following adverse drug events may be borne in mind as potential effects of acetaminophen: allergic reactions, rash, thrombocytopenia, agranulocytosis.

Potential effects of high dosage are listed in the OVERDOSAGE section.

DRUG ABUSE AND DEPENDENCE

Controlled Substance: Hydrocodone Bitartrate and Acetaminophen Tablets are classified as Schedule III controlled substance.

Abuse and Dependence: Psychic dependence, physical dependence, and tolerance may develop upon repeated administration of narcotics; therefore, this product should be prescribed and administered with caution. However, psychic dependence is unlikely to develop when hydrocodone bitartrate and acetaminophen tablets are used for a short time for the treatment of pain.

Physical dependence, the condition in which continued administration of the drug is required to prevent the appearance of a withdrawal syndrome, assumes clinically significant proportions only after several weeks of continued narcotic use, although some mild degree of physical dependence may develop after a few days of narcotic therapy. Tolerance, in which increasingly large doses are required in order to produce the same degree of analgesia, is manifested initially by a shortened duration of analgesic effect, and subsequently by decreases in the intensity of analgesia. The rate of development of tolerance varies among patients.

OVERDOSAGE

Following an acute overdosage, toxicity may result from hydrocodone or acetaminophen.

Signs and Symptoms

Hydrocodone: Serious overdose with hydrocodone is characterized by respiratory depression (decrease in respiratory rate and/or tidal volume, Cheyne-Stokes respiration, cyanosis), extreme

= Brand Name /
Generic Name

AND A Product

Listed Drug

stupor or coma, skeletal muscle flaccidity, cold and clammy skin, and sometimes bradycardia and hypotension. In severe overdose, apnea, circulatory collapse, cardiac arrest, and death may occur.

Acetaminophen: In acetaminophen overdosage: dose-dependent, potentially fatal hepatic necrosis is the most serious adverse effect. Renal tubular necrosis, hypoglycemic coma, and thrombocytopenia may also occur.

Early symptoms following a potentially hepatotoxic overdose may include: nausea, vomiting, diaphoresis, and general malaise. Clinical and laboratory evidence of hepatic toxicity may not be apparent until 48 - 72 hours post-ingestion.

In adults, hepatic toxicity has rarely been reported with acute overdose of less than 10 grams, or fatalities with less than 15 grams.

Treatment: A single or multiple overdose with hydrocodone and acetaminophen is a potentially lethal polydrug overdose, and consultation with a regional poison control center is recommended.

Immediate treatment includes support of cardio-respiratory function and measures to reduce drug absorption. Vomiting should be induced mechanically, or with syrup of ipecac, if the patient is alert (adequate pharyngeal and laryngeal reflexes). Oral activated charcoal (1g/kg) should follow gastric emptying. The first dose should be accompanied by an appropriate cathartic. If repeated doses are used, the cathartic might be included with alternate doses as required. Hypotension is usually hypovolemic and should respond to fluids. Vasoconstrictors and other supportive measures should be employed as indicated. A cuffed endo-tracheal tube should be inserted before gastric lavage of the unconscious patient and, when necessary, to provide assisted respiration.

Meticulous attention should be given to maintaining adequate pulmonary ventilation. In severe cases of intoxication, peritoneal dialysis, or preferably hemodialysis may be considered. If hypo-prothrombinemia occurs due to acetaminophen overdose, vitamin K should be administered intravenously.

Naloxone, an opioid antagonist, can reverse respiratory depression and coma associated with opioid overdose. Naloxone hydrochloride 0.4 mg to 2 mg is given parenterally. Since the duration of action of hydrocodone may exceed that of the naloxone, the patient should be kept under continuous surveillance and repeated doses of the antagonist should be administered as needed to maintain adequate respiration. A opioid antagonist should not be administered in the absence of clinically significant respiratory or cardiovascular depression.

symptoms progressing to stupor or coma, skeletal muscle flaccidity, cold and clammy skin, and sometimes bradycardia and hypotension. In severe overdosage, apnea, circulatory collapse, cardiac arrest and death may occur.

Acetaminophen: In acetaminophen overdosage: dose-dependent, potentially fatal hepatic necrosis is the most serious adverse effect. Renal tubular necrosis, hypoglycemic coma, and thrombocytopenia may also occur.

Early symptoms following a potentially hepatotoxic overdose may include: nausea, vomiting, diaphoresis and general malaise. Clinical and laboratory evidence of hepatic toxicity may not be apparent until 48 to 72 hours post-ingestion.

In adults, hepatic toxicity has rarely been reported with acute overdoses of less than 10 gram or fatalities with less than 15 grams.

Treatment: A single or multiple overdose with hydrocodone and acetaminophen is a potentially lethal polydrug overdose, and consultation with a regional poison control center is recommended.

Immediate treatment includes support of cardiorespiratory function and measures to reduce drug absorption. Vomiting should be induced mechanically or with syrup of ipecac if the patient is alert (adequate pharyngeal and laryngeal reflexes). Oral activated charcoal (1 g/kg) should follow gastric emptying. The first dose should be accompanied by an appropriate cathartic. If repeated doses are used, the cathartic might be included with alternate doses as required. Hypotension is usually hypovolemic and should respond to fluids. Vasoconstrictors and other supportive measures should be employed as indicated. A cuffed endotracheal tube should be inserted before gastric lavage of the unconscious patient and, when necessary, to provide assisted respiration.

Meticulous attention should be given to maintaining adequate pulmonary ventilation. In severe cases of intoxication, peritoneal dialysis, or preferably hemodialysis may be considered. If hypoprothrombinemia occurs due to acetaminophen overdose, vitamin K should be administered intravenously.

Naloxone, a narcotic antagonist, can reverse respiratory depression and coma associated with opioid overdose. Naloxone hydrochloride 0.4 mg to 2 mg is given parenterally. Since the duration of action of hydrocodone may exceed that of the naloxone, the patient should be kept under continuous surveillance and repeated doses of the antagonist should be administered as needed to maintain adequate respiration. A narcotic antagonist should not be administered in the absence of clinically significant respiratory or cardiovascular depression.

ANDA Product

Listed Drug

If the dose of acetaminophen may have exceeded 140 mg/kg, acetylcysteine should be administered as early as possible. Serum acetaminophen levels should be obtained, since levels four or more hours following ingestion help predict acetaminophen toxicity. Do not await acetaminophen assay results before initiating treatment. Hepatic enzymes should be obtained initially, and repeated at 24-hour intervals.

Methemoglobinemia over 30% should be treated with methylene blue by slow intravenous administration.

The toxic dose for adults for acetaminophen is 10 g.

DOSAGE AND ADMINISTRATION

Dosage should be adjusted according to severity of pain and response of the patient. However, it should be kept in mind that tolerance to hydrocodone can develop with continued use and that the incidence of untoward effects is dose related.

The usual adult dosage is two tablespoonfuls (30 mL) every four to six hours as needed for pain. The total 24-hour dose should not exceed 6 tablespoons.

HOW SUPPLIED

Hydrocodone Bitartrate and Acetaminophen Elixir is a clear, fruit flavored liquid containing 10 mg hydrocodone bitartrate, and 650 mg acetaminophen per 30 mL, with 7% alcohol. It is supplied as follows:

10mg/650 mg per 30 mL:
16 oz. Bottles
4 oz. Bottles
30 mL Unit Dose Cups

NDC 0121-0718-16
NDC 0121-0718-04
NDC 0121-0718-30

Store at controlled room temperature 20°-25°C (68°-77°F).

Dispense in a tight, light-resistant container.

R_x ONLY

A Schedule III controlled substance

PHARMACEUTICAL ASSOCIATES, INC.
Greenville, SC

02/00

Watson Laboratories
Corona, CA 91720

Revised December 15, 1997
13100-1

If the dose of acetaminophen may have exceeded 140 mg/kg, acetylcysteine should be administered as early as possible. Serum acetaminophen levels should be obtained, since levels four or more hours following ingestion help predict acetaminophen toxicity. Do not await acetaminophen assay results before initiating treatment. Hepatic enzymes should be obtained initially, and repeated at 24-hour intervals.

Methemoglobinemia over 30% should be treated with methylene blue by slow intravenous administration.

The toxic dose for adults for acetaminophen is 10 g.

DOSAGE AND ADMINISTRATION

Dosage should be adjusted according to the severity of the pain and the response of the patient. However, it should be kept in mind that tolerance to hydrocodone can develop with continued use and that the incidence of untoward effects is dose related.

The usual adult dosage is one or two tablets every four to six hours as needed for pain. The total daily dosage should not exceed 8 tablets.

The usual adult dosage is one or two tablets every four to six hours as needed for pain. The total daily dosage should not exceed 8 tablets.

The usual adult dosage is one tablet every four to six hours as needed for pain. The total daily dosage should not exceed 6 tablets.

The usual adult dosage is one tablet every four to six hours as needed for pain. The total daily dosage should not exceed 5 tablets.

The usual adult dosage is one tablet every four to six hours as needed for pain. The total daily dosage should not exceed 6 tablets.

The usual adult dosage is one tablet every four to six hours as needed for pain. The total daily dosage should not exceed 6 tablets.

The usual adult dosage is one tablet every four to six hours as needed for pain. The total daily dosage should not exceed 6 tablets.

HOW SUPPLIED

Hydrocodone Bitartrate and Acetaminophen Tablets are supplied in the following strengths:

2.5 mg hydrocodone bitartrate and 500 mg acetaminophen, orange-white tablets bisected on one side and debossed with Watson 388 on the other side.

Bottles of 30 NDC 52544-388-30
Bottles of 100 NDC 52544-388-01
Bottles of 500 NDC 52544-388-05
Bottles of 1000 NDC 52544-388-10

5 mg hydrocodone bitartrate and 500 mg acetaminophen, capsule-shaped white tablets bisected on one side and debossed with Watson 345 on the other side.

Bottles of 30 NDC 52544-345-30
Bottles of 100 NDC 52544-345-01
Bottles of 500 NDC 52544-345-05

7.5 mg hydrocodone bitartrate and 500 mg acetaminophen, capsule-shaped white tablets bisected on one side and debossed with Watson 365 on the other side.

Bottles of 30 NDC 52544-365-30
Bottles of 100 NDC 52544-365-01
Bottles of 500 NDC 52544-365-05
Bottles of 1000 NDC 52544-365-10

7.5 mg hydrocodone bitartrate and 750 mg acetaminophen, oblong white tablets bisected on one side and debossed with Watson 337 on the other side.

Bottles of 30 NDC 52544-337-30
Bottles of 100 NDC 52544-337-01
Bottles of 500 NDC 52544-337-05
Bottles of 1000 NDC 52544-337-10

7.5 mg hydrocodone bitartrate and 650 mg acetaminophen, capsule-shaped, pink tablets bisected on one side and debossed with Watson 502 on the other side.

Bottles of 100 NDC 52544-502-01
Bottles of 500 NDC 52544-502-05

10 mg hydrocodone bitartrate and 500 mg acetaminophen, capsule-shaped, blue tablets bisected on one side and debossed with Watson 540 on the other side.

Bottles of 100 NDC 52544-540-01
Bottles of 500 NDC 52544-540-05

10 mg hydrocodone bitartrate and 650 mg acetaminophen, capsule-shaped, light green tablets bisected on one side and debossed with Watson 503 on the other side.

Bottles of 100 NDC 52544-503-01
Bottles of 500 NDC 52544-503-05

Store at controlled room temperature 15°-30°C (59°-86°F).
Dispense in a tight, light-resistant container with a child-resistant closure.

= Brand Name / Generic Name

= changed due to dosage form

= Controlled Room Temperature changed to current USP 24

Exhibit D

ANDA Product

Listed Drug

FRONT OF LABEL:

NDC 0121-0718-16

**HYDROCODONE BITARTRATE
AND ACETAMINOPHEN ELIXIR**

III

10 mg/650 mg per 30 mL

Hydrocodone bitartrate, USP
(Warning: May be habit forming)

10 mg

Acetaminophen, USP

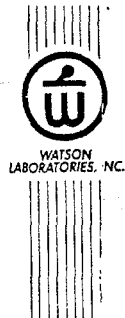
650 mg

Alcohol 7 %

Rx ONLY

16 fl oz (473 mL)

PHARMACEUTICAL ASSOCIATES, INC.
GREENVILLE, SC 29605



NDC 52544-503-01

**HYDROCODONE
BITARTRATE and
ACETAMINOPHEN
TABLETS, USP**

10 mg/650 mg

Each Tablet Contains:
Hydrocodone Bitartrate, USP 10 mg
(Warning: May be habit forming)
Acetaminophen, USP 650 mg

CAUTION: Federal law prohibits
dispensing without prescription.

100 TABLETS



Dispense in a tight, light-resistant container with a child-resistant closure.
Usual Adult Dosage: One tablet every four to six hours as needed for pain. Usual daily dosage should not exceed six tablets. See insert for full prescribing information. Keep this and all medication out of the reach of children. Store at controlled room temperature 20°-25° C (68°-77° F).

Watson Laboratories, Inc.
Corona, CA 91720

12592



N 3 52544-503-01 2

Lot No.: 50308E99
Exp: 5/2001

RIGHT SIDE OF LABEL:

USUAL DOSAGE: See package insert
for complete prescribing information.
Lot No.
Exp. Date

= Brand Name / Generic Name

LEFT SIDE OF LABEL:

Pharmacist: Dispense in a tight, light-resistant
container as defined in the USP, with a
child-resistant closure (as required).

Store at controlled room temperature
20°-25° C (68°-77° F)

? = change due to dosage form


 = Controlled Room Temperature
changed to current USP 24



Exhibit E

15 mL Tray Label

NDC 0121-0718-30

**HYDROCODONE BITARTRATE
AND ACETAMINOPHEN ELIXIR**

10 mg/ 650 mg per 30 mL

Alcohol 7%

Preservative: Methylparaben 0.15%

pH Range: 4.0 – 5.0

Usual Dosage: See Package Insert for
Complete Dosage Recommendations.

10 × 30 mL

This unit-dose package is not child-resistant.

Store at controlled room temperature,

20° - 25° C (68° - 77° F)

R_x ONLY

FOR INSTITUTIONAL USE ONLY
PHARMACEUTICAL ASSOCIATES, INC.

GREENVILLE, SC 29605

4 oz. Bottle Label

FRONT OF LABEL:

NDC 0121-0718-04

**HYDROCODONE BITARTRATE
AND ACETAMINOPHEN ELIXIR**

CIII

10 mg /650 mg per 30 mL

Hydrocodone bitartrate, USP

10 mg

(Warning: May be habit forming)

Acetaminophen, USP

650 mg

Alcohol 7 %

R_x ONLY

4 fl oz (118 mL)

PHARMACEUTICAL ASSOCIATES, INC.
GREENVILLE, SC 29605

RIGHT SIDE OF LABEL:

USUAL DOSAGE: See package insert
for complete prescribing information.

Lot No.

Exp. Date

LEFT SIDE OF LABEL:

Pharmacist: Dispense in a tight, light-resistant
container as defined in the USP, with a
child-resistant closure (as required).
Store at controlled room temperature
20° - 25° C (68° - 77° F)

16 oz. Bottle

FRONT OF LABEL:

NDC 0121-0718-16

**HYDROCODONE BITARTRATE
AND ACETAMINOPHEN ELIXIR**

CIII

10 mg /650 mg per 30 mL

Hydrocodone bitartrate, USP
(Warning: May be habit forming)
Acetaminophen, USP
Alcohol 7 %
R_x ONLY

10 mg

650 mg

16 fl oz (473 mL)

PHARMACEUTICAL ASSOCIATES, INC.
GREENVILLE, SC 29605

RIGHT SIDE OF LABEL:

USUAL DOSAGE: See package insert
for complete prescribing information.

Lot No.

Exp. Date

LEFT SIDE OF LABEL:

Pharmacist: Dispense in a tight, light-resistant
container as defined in the USP, with a
child-resistant closure (as required).
Store at controlled room temperature
20° - 25° C (68° - 77° F)

Hydrocodone bitartrate and Acetaminophen Elixir (NDC 0121-0718-) has been packaged in the following container/closure systems:

1. Bottle: 16 oz. Amber PET 28-400 container
Cap: 28-400 White Fine Ribbed P/P Closure with P/RVTLF Liner
2. Bottle: 16 oz. Amber PET 28-400 container
Cap: 28-400 White Fine Ribbed Closure with SG-90 Liner
3. Bottle: 16 oz. Brown HDPE BL-16 container
Cap: 28-400 White Fine Ribbed P/P Closure with P/RVTLF Liner
6. Bottle: 4 oz. Amber PET 24-400 container
Cap: 24-400 White Clic-Loc with P/RVTLF Liner
7. Unit Dose Cup: BP 15 HDPE Unit Dose Container made of Alathon resin.
Lidding: Paper/Polyethylene/Aluminum Foil/Heat Seal by Tekni-Plex

We intend to seek approval for all container / closure systems except the Unit Dose Cup BP 10.